Remarks

Claims 1-28, 30-35, 37-88, 96 and 99-115 are pending.
Claims 1, 9-11, 45, 59-60, 75, 78-80, 103-106 and 114 are presently amended.

The Examiner has raised a number of issues in the Office Action regarding claim language and has also provided helpful suggestions from resolving such issues. Applicants wish to thank the Examiner for providing such helpful suggestions in an effort to expedite the prosecution of this application. In those instances where Applicants have adopted the Examiner's suggested language, this is noted within the following remarks. Support for all the above claim amendments is present in the application as filed, as will be pointed out in the following remarks discussing the various amendments. There being no issues of new matter, entry of the foregoing amendments is respectfully requested.

At pages 2-7 of the Office Action, Claims 1-28, 30-35, 37-88, 96 and 99-115 are rejected under 35 USC 112, second paragraph, as being indefinite. A number of issues are raised regarding claim language with respect to particular claims. These are addressed in the order presented in the Office Action.

(1) Claim 1 - The Examiner states that the claim language "wherein Het is a five . . . including aromatic" is indefinite for leaving the metes and bounds undefined.

In response, Applicants have amended claim 1 at this location to state that the Het is a "five-, six-, or seven-membered saturated or unsaturated, aromatic or non-aromatic, heterocycle containing . . .". Applicants submit that this language is definite. Support for including both aromatic and non-aromatic heterocycles is found, e.g., at page 12, lines 9-19 where numerous aromatic and non-aromatic examples of Het are provided in the definition of Het.

(2) Claim 1 – the Examiner points out that certain language with respect to the R_{12} and

R_{12a} definition is grammatically incorrect. Applicants appreciate this careful review and have amended the claims as suggested by the Examiner to resolve this issue.

(3) Claims 9-11 – The Examiner points out that the references to "D" or "L" amino acids when reciting the side chains thereof is inappropriate since the "side chain" does not include the chiral center. The Examiner has kindly provided suggested claim language which Applicants have adopted in amending claims 9-11 in order to resolve this issue. Support for this amendment is found in the original claim language.

(4) Claims 17 and 77-79 – The Examiner argues that the terms (e.g., "Tbg") are undefined. The abbreviations used in the claims are in fact defined in the specification and the claims must be read in light of the specification. The Examiner's attention is respectfully directed to Table A at page 8 for definitions for various abbreviations used in the claims, including Tbg.

(5) Claims 45, 59, 60 – The Examiner argues that these claims are rendered indefinite by the recitation "racemic mixture of diastereoisomers" in view of the technical meanings of "racemate" and "diastereoisomer".

In response, Applicants have amended claim 45 to recite "or a racemate, a diastereoisomer or an optical isomer thereof", support being found in the original claim language. Applicants submit that this revised claim language is clear as to the coverage intended and this is the identical claim language found in claims 1 and 67, which were both found to be acceptable by the Examiner.

Applicants have amended claims 59-60 to recite "a racemic mixture of two stereoisomers", support being found in the original claim. Applicants submit that this revised claim language is clear as to the coverage intended, in view of the depictions of the racemate and the two stereoisomers within the racemic mixture.

(6) Claim 75 – The Examiner argues that the abbreviations "Acca" and "Np" appear but are not defined in the claim. The abbreviations used in the claims are in fact defined in the specification and the claims must be read in light of the specification. The Examiner's attention is respectfully directed to Table A at page 8 for definition of Acca and to page 113, lines 25-26, for the definition of the 1-NpCH_2O group recited in the claim.

(7) Claim 75 – The Examiner points out that the location of the "P3" group is not entirely clear since it is not identified in the structure. In response, claim 75 is amended to include the P2 to P4 groups, support being found in the structural depictions present throughout the application as filed.

(8) Claim 79 – The Examiner points out that "selected from ..." is improper since only one compound is claimed. This claim has been amended appropriately to resolve this issue.

(9) Claim 80 – the Examiner argues that "Dnl" is undefined. In response, the two compounds reciting Dnl (compounds 702 and 911) have both been deleted from the claims, rendering this rejection moot.

(10) Claim 106 – The Examiner argues that the term "cleavable" renders the process indefinite as to whether cleavage takes place. In response, the Examiner's attention is respectfully directed to the language in step (3) of each of the parent claims 103 to 105 from which claim 106 depends, which clearly state that the CPG group is cleaved, i.e. "cleaving the CPG . . .". Thus, it is clear that cleavage of the CPG does take place during the claimed process and, therefore, the recited claim language is not indefinite.

(11) Claim 106 – the Examiner argues that the carboxyl protecting groups are "esters" is inappropriate since the CPG group is not itself an ester but rather forms an ester with the carboxyl group to which it is bonded. In response, this claim has been

amended to delete the term "ester" as this is inappropriate to define the CPG group per se, as pointed out by the Examiner. As claimed, the CPG group is an alkyl, an aralkyl or a group being cleavable by mild base treatment or mild reductive means. Such groups as CPGs are supported by the original claim language and the description at page 41, lines 22-27, as clearly understood by a person skilled in the art.

(12) Claims 103-106 – The Examiner argues that the process claims are rendered indefinite by their failure to recite a step for isolating the final product. In response, these claims are amended to include an isolation step in the last step of the process, support being inherent in the process descriptions and examples in the application as filed directed to the preparation of compounds of formula (I).

(13) Claim 114 – The Examiner argues that "ribavirin" may be used if accompanied by the chemical name that this term represents. Applicants point out that the application, including the claims, must always be read as they would be by one having ordinary skill in the art who would understand the conventional meanings of terms not specifically defined in the application as filed. One skilled in the art would clearly understand what is meant by ribavirin, as this was a commonly known antiviral agent at the time the present application was filed. This is evidenced by the enclosed page from a 1986 review article in Antimicrobial Agents and Chemotherapy (see the highlighted text in the Introduction). In any event, in order to facilitate allowance, Applicants have amended claim 114 to also include the chemical name for ribavirin, as supported by the enclosed pre-filing date review article.

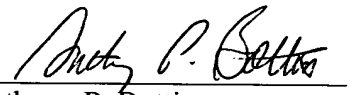
(14) Claim 114 – the Examiner argue that claim 114 requires a component not required by claim 99 and therefore the propriety of claim dependence is called into question. Applicants submit that the claim dependency is correct and therefore no further amendment is necessary. Parent claim 99 is a combination "comprising" a compound of formula I and other ingredients as recited. Since "comprising" is the standard open-ended transitional term, claim 99 clearly allows for the presence of unspecified

ingredients, including the ribavirin recited in dependent claim 114. Thus, Applicants submit that claim dependency is proper.

In view of the above amendments and remarks, Applicants respectfully submit that the claims are definite and in compliance with 35 USC 112, second paragraph. The Examiner is therefore requested to withdraw this rejection.

Applicants submit that this application is now in condition for allowance. If any questions should arise regarding this application, the Examiner is invited to contact the undersigned attorney at the telephone number provided below.

Respectfully submitted,



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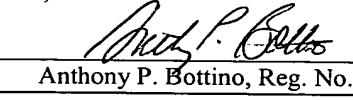

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MINIREVIEW

Biochemistry and Clinical Applications of Ribavirin

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INTRODUCTION

Over the past few years, many nucleoside analogs have been synthesized in the search for new antiviral agents. Of the few that have been useful as antiviral agents, most have a limited range of in vitro effectiveness. However, ribavirin (1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide; M_r, 244.200) is an antiviral agent that has shown in vitro activity against a broad spectrum of DNA and RNA viruses (8, 20, 34). This antiviral activity is due to the resemblance of this compound to nucleosides. Ribavirin has shown clinical efficacy against both influenza A and B virus (12, 21, 27), respiratory syncytial virus (RSV) (11, 15, 16, 29), and parainfluenza virus infections (11, 29) and Lassa fever (28). Ribavirin is in clinical trials to test its effectiveness against herpesvirus, human T-cell lymphotropic virus type III/lymphadenopathy-associated virus, and a variety of exotic viral diseases. In this report, we summarize the current data on ribavirin as to chemical structure, possible mode(s) of action, metabolic disposition, and clinical use as an antiviral agent.

STRUCTURAL AND BIOCHEMICAL CHARACTERISTICS OF RIBAVIRIN

In 1972, ribavirin was synthesized by chemically combining derivatives of 1,2,4-triazole-3-carboxamide and ribofuranoside (49) and shown to have promise as a broad-spectrum antiviral agent (35). Subsequent studies showed that ribavirin most closely resembles guanosine, as determined by X-ray crystallography (Fig. 1) (31). Although not all enzyme systems utilize ribavirin as they do guanosine, it has been shown that many of the systems that are inhibited by ribavirin are reversed by the addition of guanosine (38). An important exception is adenosine kinase, which traps ribavirin within the cell (41, 46) but does not utilize guanosine as a substrate (30).

The antiviral activity of ribavirin is quite specifically associated with its structure. Alterations to either the ribose moiety or to the base result in a substantial loss of antiviral activity (38). However, additions to the hydroxyl groups (e.g., acetylation, phosphorylation) or conversion of the carboxamide group on the triazole to a carboxamidine retains antiviral activity, presumably due to the biological conversion of these compounds back to ribavirin. Ribavirin triacetate has been shown to be more effective than ribavirin in the treatment of dengue virus and Colorado tick fever virus encephalitis in experimental animals (23, 36). It has been suggested that the hydrophobic nature of the triacetate form allows ribavirin to remain longer in tissues and to cross the blood-brain barrier.

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The intracellular metabolism of ribavirin has been studied most extensively in L5178Y lymphoma cells and in human and monkey erythrocytes (5, 33, 52). Ribavirin is converted to its 5'-phosphate derivatives by cellular enzymes. The major metabolite is ribavirin-5'-triphosphate (RTP), and the intracellular concentration of the mono-, di-, and triphosphate derivatives probably is similar to that of other nucleotides (i.e., 1:5:25, respectively). The intracellular concentration of RTP in lymphoma cells approximates that in the extracellular environment. Erythrocytes, however, concentrate RTP, for they are not able to efficiently dephosphorylate ribavirin. This accumulation of ribavirin is believed to play a role in the transient anemia that has been observed with some high-dosage regimens (28, 33).

MECHANISM OF ACTION OF RIBAVIRIN

The mechanism of the antiviral effect of ribavirin has been studied in detail only for the influenza viruses (38, 50, 51). Based on these and other studies, three possible mechanisms of action for ribavirin have been proposed: a decrease in the intracellular concentration of GTP due to competitive inhibition of IMP dehydrogenase and two virus-specific actions, inhibition of 5'-cap formation of mRNAs and inhibition of the function of virus-coded RNA polymerases necessary to prime (initiate) and elongate viral mRNAs.

Ribavirin-5'-monophosphate is a potent inhibitor of IMP dehydrogenase activity in purified enzyme preparations from either P388 or Erlich ascites cells (42). Cells treated with ribavirin have decreased GTP pools (43, 51), presumably due to this inhibition. Thus, competition for the remaining GTP by cellular and viral enzymes may play a role. However, GTP pools alone cannot totally explain the antiviral effect. Wray et al. (51) showed that the anti-influenza virus activity of ribavirin increases progressively with reduction in GTP intracellular pools up to 25 μM. As ribavirin concentrations were further increased, the antiviral effect progressively

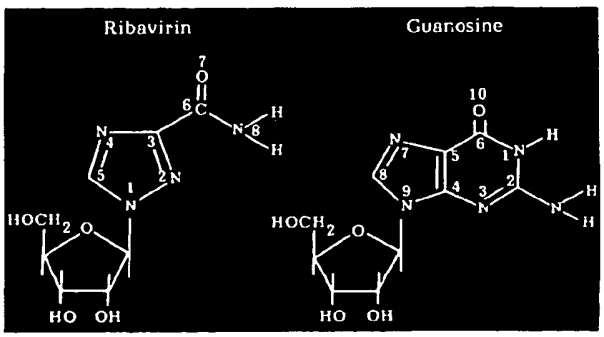

FIG. 1. Chemical structure of ribavirin and guanosine.